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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL THIAZOLIDINONES HETEROCYCLIC COMPOUNDS

BIRAJDAR MJ*[1], SATPUTE KL[1], SONVANE SM[1], PHULARI AR[2], GADGUL AB[1] AND LOHIYA GV[1]

1: Dayanand Education Society's, Dayanand College of Pharmacy, Latur, Maharashtra, India

2: Aurobindo Pharma Ltd, Hyderabad, India

*Corresponding Author: Mr. Mahesh J Birajdar: E Mail: bmahesh1686@gmail.com

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ABSTRACT

The last 20 years have seen a significant increase in interest in substituted thiazolidinones due to their diverse biological activities and multitude of medicinal applications. To sum up, we want to create novel, extremely effective substituted thiadiazole molecules with minimal side effects. The current study produces thiazolidene-2, 4-dione by refluxing thiourea and chloroacetic acid for 40 hours. The scaffold for thiadiazole is produced by this technique. 5-(4-ethoxybenzylidene)-1,3-thiazolidine-2,4-dione was produced by refluxing thiazolidine-2,4-dione with 4-ethoxybenzaldehyde and sodium acetate in glacial acetic acid medium for 12 hours. The final scaffold was created by combining 5-(4-ethoxybenzylidene)-1, 3-thiazolidine-2, 4-dione with substituted 2-aminopyridine utilizing the Mannich base reaction. These compounds that were produced were examined using LC-MS, HNMR, and IR spectroscopy. The disc-diffusion technique was utilized to evaluate anti-bacterial activity these synthetic compounds. Anti-inflammatory activity of synthesized compounds screened by carrageenan induced paw oedema model & Eddy's hot plate method where used for analgesic activity.

Keyword: Anti-bacterial activity, Thizolodine, 2-amino pyridine, Disc-diffusion method

INTRODUCTION:-

Most diseases in the modern world are brought on by pathogenic organisms like viruses, bacteria, fungus, and ricketsia. Numerous potent and broad-spectrum antibiotics were created to address these ailments. Even while antibiotics are drugs that can save lives, they can sometimes be harmful. Hyper-infection, the development of resistance, the elimination of the typical non-pathogenic bacterial flora, allergic and anaphylactic reactions, and selective toxicity, including plastic anemia and kidney damage, are some of these effects **[1-2]**. Medication resistance to various antibiotics and other drugs is one of the biggest problems facing investigators. It is imperative that new medications be developed in order to counteract these increases. Additionally, it is noted that insufficient time is required to develop resistance. These create morbidity and cause higher health costs **[3-5]**.

The research indicates that heterocyclic molecules containing nitrogen and sulphur atoms have a wide range of biological and pharmacological uses. As a result, these heterocycles appeal to several researchers **[6]**. The thiazolidinedione nucleus is involved in a wide range of biological processes, including defence against microbes, viruses, convulsions, cancer, inflammation, tuberculosis, and pain. These days, the focus of research is on developing and synthesizing new thiazolidinedione nuclei with anti-inflammatory, anti-tubercular, anti-diabetic, antibacterial, anti-oxidant, and anti-cancer properties **[7-8]**. When used against different gram-positive and gram-negative bacteria, the thiazolidinedione exhibits encouraging bactericidal efficacy. The thiazolidinones ability to inhibit bacteria is dependent on its replacements **[9–11]**. Our work was primarily focused on the synthesis and characterization of heterocycles called thiazolidinones that include nitrogen and sulphur atoms. Additionally, we biologically screened these scaffolds for antibacterial, analgesic, and anti-inflammatory properties.

Experimental:-

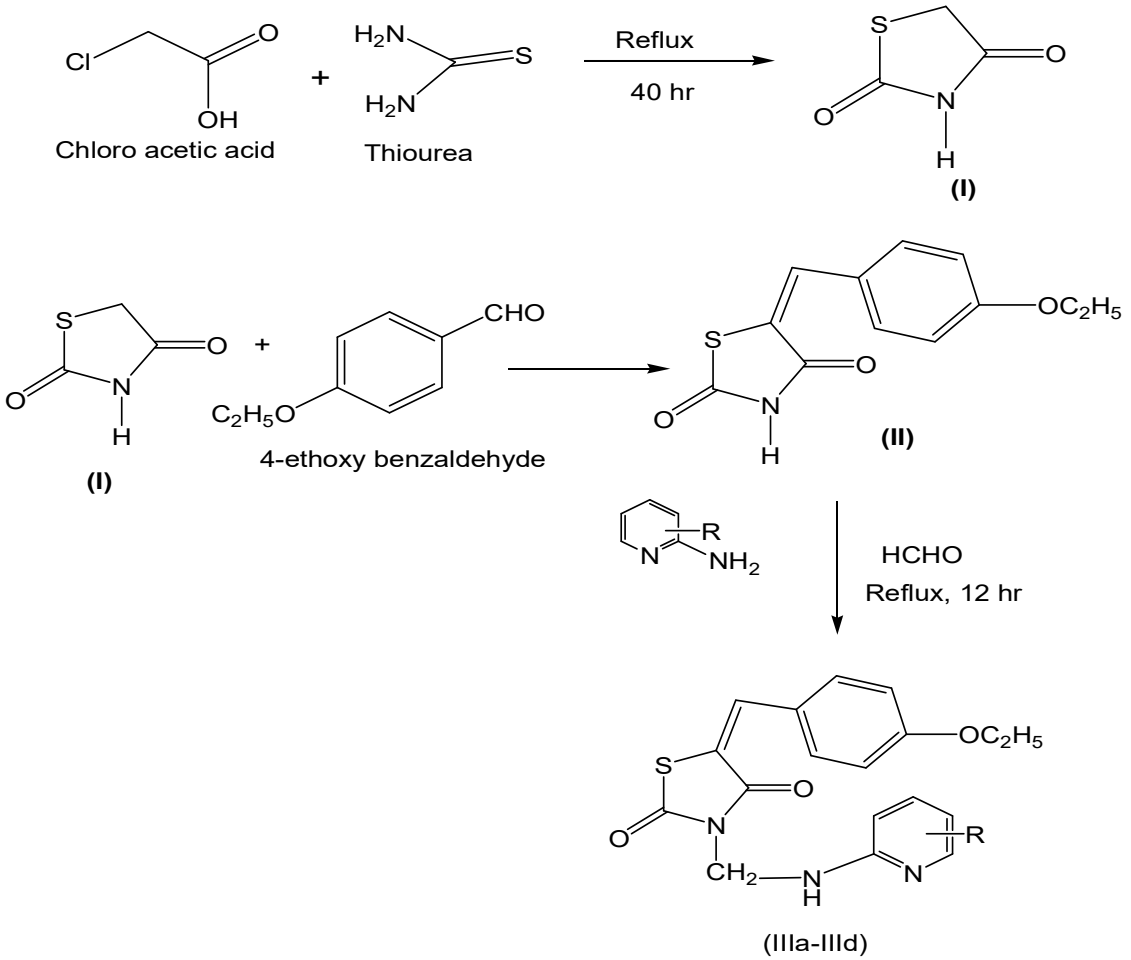

Figure 1: Scheme for synthesis of Heterocyclic compounds

Procedure for the preparation of thiazolidene-2, 4-dione (I):

A solution of 0.106 mol of thiourea and 0.106 mol of chloroacetic acid in 15 ml of water was refluxed for 40 hours in a 100 ml clean, dry round-bottom flask. After being recrystallized from water, the resultant product, thiazolidene-2,4-dione (1), had a 50% yield and a melting point of 120 º C.

Procedure for the preparation of 5-(4-ethoxybenzylidene)-1,3-thiazolidene-2,4-dione (II):

Thiazolidene-2,4-dione (1 mol, 1.17 gm) (I) was dissolved in 10 ml of glacial acetic acid in a 100 ml clean and dry round-bottom flask. 4-Ethoxybezaldehyde (1.1 mol, 1.65 ml) and sodium acetate (1.5 mol, 1.23 gm) were then added, and the reaction mixture was refluxed for 12 hours. The mixture was allowed to cool to room temperature once the reaction was finished, and the separated solid was filtered, cleaned with water, and dried. After being recrystallized from ethanol, the resulting benzylidene derivative

(II) had a 90% yield and a melting point of 182-184 ºC.

Procedure for the preparation of 5-(4-ethoxybezylidene)-3[(pyridine-2-ylamino) methyl]-1, 3-thiazolidene-2, 4-dione (IIIa):

5-(4-ethoxybenzylidene)-1,3-thiazolidene-2,4-dione (0.002 mol, 0.5 gm) (II) was dissolved in enough ethanol in a 50 ml clean, dry round-bottom flask. 3–4 drops of concentrated HCl were then added drop wise, and the reaction mixture was kept stirring with the aid of a magnetic stirrer. Formaldehyde (0.002 mol, 0.2 ml) was added drop wise to the stirring reaction mixture, and stirring was maintained continuously for a while. After adding the dissolved 2-aminopyridine (0.002 mol, 0.19 gram) in ethanol to the reaction mixture above, stirring was continued for a further 15-20 minutes, and reflux was allowed to occur for a full 12-hour period. Following the reaction's conclusion, the mixture was allowed to cool to room temperature before the separated solid was dried and filtered. IIIa, the resultant product, was recrystallized from suitable solvent. The other Mannich bases of this series i.e. **(III b – IIId)** were prepared by using appropriate 2-amino pyridine following the procedure as above and the data was given in the **Table 1**.

PHARMACOLOGICAL DATA:-

The produced substances were examined for their ability to operate as an antibacterial, analgesic, and anti-inflammatory. Four common microorganisms—Bacillus subtilis, Bacillus pumilis, Escherichia coli, and pseudomonas aeruginosa—were used to test the anti-bacterial activity of the synthesized chemicals **[12]**. These species represent gram positive and gram negative, respectively. Using the disc diffusion method, the compounds' antibacterial activity was evaluated. Ciprofloxacin was employed as a standard and evaluated at 50 and 100 µg/ml for antibacterial activity. Diclofenac sodium was utilized as a reference to test the anti-inflammatory properties of produced compounds using a carrageenan-induced paw oedema model in rats. The animals were divided into six distinct groupings. Group II is the standard group and Group I is the control group. Group I receives a dosage of 20 mg/kg of Diclofenac Sodium. Group III to Group For synthetic compounds, a 200 mg/kg dosage was generated in 1% acacia gum suspension, and Eddy's hot plate method was used to test the analgesic effect of the compounds by screening their biological activity against a reference dose of 35 mg/kg of Pentazocine **[13]**.

RESULT & DISCUSSION:-

The synthesised derivatives of thizolodine gave very good percentage yield and melting

points were determined by using Toshniwal apparatus in open capillaries and are uncorrected. Further synthesised compounds confirmed by IR, H-NMR and LC-MS spectroscopy.

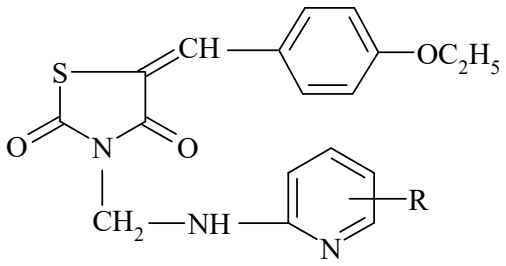

Table 1: Physicochemical data of synthesised compounds

Sr. No	Compound code	R	Molecular Formula	Molecular Weight	Melting Point (°C)	R^f value	Yield (%)
1	IIIa	H	$C_{18}H_{17}N_3O_3S$	355	142-144	0.84	58
2	IIIb	3-CH_3	$C_{19}H_{19}N_3O_3S$	369	94-96	0.68	62
3	IIIc	4-CH_3	$C_{19}H_{19}N_3O_3S$	369	152-154	0.56	49
4	IIId	6-CH_3	$C_{19}H_{19}N_3O_3S$	369	146-148	0.72	53

The purity of the synthesised compounds was checked by TLC by using chloroform: ethyl acetate (7:3) as solvent system and U.V lamp used as a visualizing agent and further characterized by IR, H-NMR and LC-MS spectroscopy.

Spectral Data of synthesized compounds:-

Spectral Data of Compound I:-

^{1}H NMR Spectra (δ ppm):12.0 (1H, s, 1H of NH) and 4.1 (2H, s, 2H of CH_2)., **IR Spectra (cm^{-1}):**3469 (NH – Stretching), 3129, 3049 (Ar-CH=CH Stretching), 2949, 2826 (CH_2-CH Stretching) and 1738 (C=O Stretching).

Spectral Data of Compound II:- ^{1}H NMR Spectra (δ ppm): 12.4 (1H, s, 1H of NH), 7.7 (1H, s, 1H of =CH), 6.9 – 7.5 (4H, m, 4H of Ar-H), 3.97 – 4.2 (2H, m, 2H of CH_2 of OC_2H_5) and 1.2 – 1.4 (3H, m, 3H of CH_3 of OC_2H_5).,**IR Spectra (cm^{-1}):**3152 (NH – Stretching), 3040, 2981 (Ar-CH=CH Stretching) and 1759, 1692 (C=O Stretching).,**MASS Spectra (m/z):** Molecular weight of the compound is 249 and molecular Wight of synthesised compounds (m-1)is appeared at 248.

Spectral Data of Compound IIIa:- ^{1}H NMR Spectra (δ ppm): 7.3 (1H, s, 1H of =CH), 6.3 – 7.2 (7H, m, 7H of Ar-H), 6.9 (1H, s, 1H of NH), 5.7 – 5.9 (2H, d, 2H of N-CH_2-N), 3.9 – 4.1 (2H, m, 2H of CH_2 of OC_2H_5), and 2.1 – 2.5 (3H, m, 3H of CH_3 of OC_2H_5)., **IR Spectra (cm^{-1}):** 3215 (NH – Stretching), 3145(CH – Stretching), 1752 (C=O Stretching) and 1587 (NH-bending).

MASS Spectra (m/z): Molecular weight of the compound is 249 and molecular Wight of synthesised compounds (m+1) is appeared at 257.

Spectral Data of Compound III c :- ^{1}H NMR Spectra (δ ppm): 7.8 (1H, s, 1H of =CH), 6.9 – 7.4 (7H, m, 7H of Ar-H), 6.6 (1H, s, 1H of NH), 5.3 – 5.4 (2H, d, 2H of N-CH_2-N), 4.0 – 4.2 (2H, m, 2H of CH_2 of OC_2H_5), 2.2 – 3.4 (3H, s, 3H of Ar-CH_3) and 1.4 – 1.5 (3H, m, 3H of CH_3 of OC_2H_5)., **IR Spectra (cm^{-1}):** 3315 (NH – Stretching), 3136, 2979 (CH – Stretching), 1735, 1710 (C=O Stretching) and 1592 (NH-bending).

Biological activity of synthesised compounds:-

Anti-bacterial activity:-

Four common bacteria, representing the symbolic types of gram positive and gram negative organisms, namely Bacillus subtilis, Bacillus pumilis, Escherichia coli, and pseudomonas aeruginosa, were used to test the chemicals generated during the current experiment. Disc diffusion was used to measure the compounds' antibacterial activity. Ciprofloxacin was employed as a standard for anti-bacterial screening, with concentrations of 100 µg/ml and 50 µg/ml.

Table 2: Anti-bacterial activity of synthesised compounds

Sample Code	*Inhibition zone diameter in mm							
	B. subtilis		*B. pumilis*		*E. coli*		*P.* aeruginosa	
	50µg	100µg	50µg	100µg	50µg	100µg	50µg	100µg
III a	6	15	9	14	8	14	10	19
III b	8	13	6	17	12	19	6	22
III c	6	22	7	15	10	17	9	14
III d	5	10	5	21	5	17	5	18
Ciprofloxacin	22	32	23	35	24	35	23	37
DMF	-	-	-	-	-	-	-	-

*Average of triplicate ± Standard deviation

Note: '-'denotes no activity, 8-12 mm poor activity, 13-17 mm moderate activity, 18-20 above good

Anti-inflammatory activity:-

The synthetic compounds under investigation, namely IIIa to IIId, were given orally to all of the rats after being evaluated for anti-inflammatory activity using conventional Diclofenac sodium. First, second, third, and fourth hour edema volumes of the injected paw were measured. The data collected were used to compute the % reduction in edema and the mean volume of oedema ± SEM.

Animals: Albino rats

Route: p.o

n=6 ns (non-significant), Significant at P< 0.05* and 0.01**.

Toxicant control compared with normal control. Standard and synthesized compounds compared with toxicant control.

ROV- Reduction in paw oedema volume.

Table 3: Anti-inflammatory activity of synthesised compounds

Groups	Treatment	Dose mg/kg	Oedema volume and percentage reduction in oedema volume at							
			1 h		2h		3h		4h	
			mean ±SEM	% ROV	mean ±SEM	% ROV	mean ±SEM	% ROV	mean ±SEM	% ROV
1	Carrageenan	0.1 ml (1% w/v)	1.33 ±0.02	-	1.37 ±0.01	-	1.38 ±0.01	-	1.37 ±0.01	-
2	Standard	30	1.31 ±0.06 ns	1.50	1.17 ±0.02**	14.6	1.04 ±0.03**	24.6	0.96 ±0.02**	29.9
3	III a	200	1.37 ±0.03 ns	3.00	1.28 ±0.03**	6.57	1.18 ±0.03**	14.5	1.04 ±0.04**	24.0
4	III b	200	1.43 ±0.03 ns	7.51	1.28 ±0.04 ns	6.57	1.13 ±0.04**	18.1	0.99 ±0.03**	27.7
5	III c	200	1.30 ±0.04 ns	2.25	1.36 ±0.04 ns	0.73	1.28 ±0.03 ns	7.24	1.23 ±0.02**	10.2
6	III d	200	1.28 ±0.05 ns	3.75	1.29 ±0.06 ns	5.83	1.22 ±0.03**	11.6	1.16 ±0.04**	15.3

Analgesic Activity:-

Technique for evaluating the central analgesic property is Eddy's hot plate approach. This technique uses heat as a painful agent. Every animal is kept individually on the hot plate at a consistent temperature of 55 ± 1 ºC. The animal's reaction time, measured by how long it takes it to lick its hind paw or jump out after setting it on the hot plate, is considered to be its response to painful stimuli. Analgesics lengthen the time needed to react. Pentazocine (35 mg/kg) was utilized as a drug of defamation for this activity. Using Eddy's hot plate, the reaction times for each mouse were noted at0,30,60,90, and 120 minutes following the injection of synthetic substances.

Animals: Albino mice
Route: p.o.

Standard drug used: Pentazocine

n=6, Significant at $p<0.05$*, 0.01** and 0.001***, ns= non-significant.

Table 4: Analgesic activity of synthesised compounds

Group	Treatment	Dose mg/kg	Basal reaction time(sec)				
			0	30	60	90	120
1	Control	10	3.83± 0.30	3.83± 0.30	4.16± 0.30	3.66± 0.33	4.28± 0.28
2	Standard	35	4± 0.25	5.16± 0.30**	7.5± 0.42	9± 0.36	8.28± 0.35
3	III a	200	4.33± 0.42	4.83± 0.30^{ns}	7.16± 0.40**	8.16± 0.30**	6± 0.25**
4	III b	200	4.16± 0.47	5.00± 0.43**	5.33± 0.21 ^{ns}	5.16± 0.30*	5.16 ±0.30 ^{ns}
5	III c	200	3.5± 0.22	3.5± 0.22 ^{ns}	5.5± 0.22 ^{ns}	5.3± 0.33**	5± 0.25 ^{ns}
6	III d	200	4± 0.25	5± 0.25*	7.3± 0.47**	7.5± 0.50**	4.6± 0.21 ^{ns}

CONCLUSION:-

Every synthetic molecule exhibits encouraging biological action. Following synthesised compounds' antibacterial activity screening. The synthetic chemicals IIIb exhibit antibacterial activity against

Escherichia coli and pseudomonas aeruginosa. Comparing compound IIIc to ciprofloxacin standard, the former is more effective against Bacillus subtilis. When compared to regular Diclofenac Sodium, the compounds III a, III b, and III c demonstrated strong anti-inflammatory action. Comparing III b to the common Pentazocine medication, it was discovered that III b exhibited good analgesic effect whereas the other chemical exhibited moderate action. The aforementioned findings demonstrate that 2-aminopyridines substituted with thiazolidinone can be further investigated in order to find novel antibacterial agents.

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